Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

Visit the AIDS*info* website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at http://aidsinfo.nih.gov/e-news.

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

Considerations for Antiretroviral Use in Patients with Coinfections

HIV/Hepatitis B Virus (HBV) Coinfection (Last updated January 10, 2011; last reviewed January 10, 2011)

Panel's Recommendations

- Prior to initiation of antiretroviral therapy (ART), all patients who test positive for hepatitis B surface antigen (HBsAg) should be tested for hepatitis B virus (HBV) DNA using a quantitative assay to determine the level of HBV replication **(AIII)**.
- Because emtricitabine (FTC), lamivudine (3TC), and tenofovir (TDF) have activity against both HIV and HBV, if HBV **or** HIV treatment is needed, ART should be initiated with the combination of TDF + FTC or TDF + 3TC as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral (ARV) regimen **(AI)**.
- If HBV treatment is needed and TDF cannot safely be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen **(BI)**. Other HBV treatment regimens include peginterferon alfa monotherapy or adefovir in combination with 3TC or FTC or telbivudine in addition to a fully suppressive ARV regimen **(BII)**.
- Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when used in HIV/HBV-coinfected patients **(AII)**.
- Discontinuation of agents with anti-HBV activity may cause serious hepatocellular damage resulting from reactivation of HBV; patients should be advised against self-discontinuation and carefully monitored during interruptions in HBV treatment **(AII)**.
- If ART needs to be modified due to HIV virologic failure and the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion*

Approximately 5%–10% of HIV-infected persons also have chronic HBV infection, defined as testing positive for HBsAg for more than 6 months.[1] The progression of chronic HBV to cirrhosis, end-stage liver disease, and/or hepatocellular carcinoma is more rapid in HIV-infected persons than in persons with chronic HBV alone.[2] Conversely, chronic HBV does not substantially alter the progression of HIV infection and does not influence HIV suppression or CD4 cell responses following ART initiation.[3-4] However, several liver-associated complications that are ascribed to flares in HBV activity, discontinuation of dually active ARVs, or toxicity of ARVs can affect the treatment of HIV in patients with HBV coinfection.[5-7] These include the following:

- FTC, 3TC, and TDF are approved ARVs that also have antiviral activity against HBV. Discontinuation of these drugs may potentially cause serious hepatocellular damage resulting from reactivation of HBV.[8]
- Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when used in HIV/HBV-coinfected patients **(AII)**.[9]
- 3TC-resistant HBV is observed in approximately 40% of patients after 2 years on 3TC for chronic HBV and in approximately 90% of patients after 4 years when 3TC is used as the only active drug for HBV in

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

coinfected patients. Therefore, 3TC or FTC should be used in combination with other anti-HBV drugs **(AII)**.[10]

- Immune reconstitution after initiation of treatment for HIV and/or HBV can be associated with elevation in transaminases, possibly because HBV is primarily an immune-mediated disease.[11]
- Some ARV agents can cause increases in transaminase levels. The rate and magnitude of these increases are higher with HBV coinfection.[12-13] The etiology and consequences of these changes in liver function tests are unclear because continuation of ART may be accompanied by resolution of the changes. Nevertheless, some experts suspend the implicated agent(s) when the serum alanine transferase (ALT) level is increased to 5–10 times the upper limit of normal. However, in HIV/HBV-coinfected persons, increases in transaminase levels can herald hepatitis B e antigen (HBeAg) seroconversion due to immune reconstitution, so the cause of the elevations should be investigated prior to the decision to discontinue medications. In persons with transaminase increases, HBeAg seroconversion should be evaluated by testing for HBeAg and anti-HBe as well as HBV DNA levels.

Recommendations for HBV/HIV-Coinfected Patients

- All patients with chronic HBV should be advised to abstain from alcohol, assessed for immunity to hepatitis A virus (HAV) infection (anti-HAV antibody total) and vaccinated if nonimmune, advised on methods to prevent HBV transmission (methods that do not differ from those to prevent HIV transmission), and evaluated for the severity of HBV infection as outlined in the Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents.[14]
- Prior to intiation of ART, all persons who test positive for HBsAg should be tested for HBV DNA using a quantitative assay to determine the level of HBV replication **(AIII)**. Persons with chronic HBV infection already receiving ART active against HBV should undergo quantitative HBV DNA testing every 6–12 months to determine the effectiveness of therapy in suppressing HBV replication. The goal of HBV therapy with NRTIs is to prevent liver disease complications by sustained suppression of HBV replication to the lowest achievable level.
- **If not yet on therapy and HBV or HIV treatment is needed:** In persons without HIV infection, the recommended anti-HBV drugs for the treatment of persons naive to HBV therapy are TDF and entecavir.[15-16] In HIV-infected patients, however, only TDF can be considered part of the ARV regimen; entecavir has weak anti-HIV activity and must not be considered part of an ARV regimen. In addition, only TDF is fully active for the treatment of persons with known or suspected 3TC-resistant HBV infection. To avoid selection of HBV-resistant variants, when possible, these agents should not be used as the only agent with anti-HBV activity in an ARV regimen **(AIII)**.

Preferred regimen. The combination of TDF + FTC or TDF + 3TC should be used as the NRTI backbone of a fully suppressive ARV regimen and for the treatment of HBV infection **(AII)**.[17-19]

Alternative regimens. If TDF cannot safely be used, entecavir should be used in addition to a fully suppressive ARV regimen **(AII)**; importantly, entecavir should not be considered to be a part of the ARV regimen[20] **(BII)**. Due to a partially overlapping HBV-resistance pathway, it is not known if the combination of entectavir + 3TC or FTC will provide additional virologic or clinical benefit compared with entecavir alone. In persons with known or suspected 3TC-resistant HBV infection, the entecavir dose should be increased from 0.5 mg/day to 1 mg/day. However, entecavir resistance may emerge rapidly in patients with 3TC-resistant HBV infection. Therefore, entecavir should be used with caution in such patients with frequent monitoring (~ every 3 months) of the HBV DNA level to detect viral breakthrough. Other HBV treatment regimens include peginterferon alfa monotherapy or adefovir in combination with 3TC or FTC or telbivudine in addition to a fully suppressive ARV regimen;[17, 21-22] however, data on these regimens in persons with HIV/HBV coinfection are limited **(BII)**. Due to safety concerns, peginterferon alfa should not be used in

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

HIV/HBV-coinfected persons with cirrhosis.

- **Need to discontinue medications active against HBV:** The patient's clinical course should be monitored with frequent liver function tests. The use of adefovir dipivoxil, entecavir, or telbivudine to prevent flares, especially in patients with marginal hepatic reserve such as persons with compensated or decompensated cirrhosis, can be considered.[8] These alternative HBV regimens should only be used in addition to a fully suppressive ARV regimen.
- **Need to change ART because of HIV resistance:** If the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression **(AIII)**.

References

1. Spradling PR, Richardson JT, Buchacz K, et al. Prevalence of chronic hepatitis B virus infection among patients in the HIV Outpatient Study, 1996-2007. *J Viral Hepat*. 2010.
2. Thio CL, Seaberg EC, Skolasky R, Jr., et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*. 2002;360(9349):1921-1926.
3. Konopnicki D, Mocroft A, de Wit S, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS*. 2005;19(6):593-601.
4. Hoffmann CJ, Seaberg EC, Young S, et al. Hepatitis B and long-term HIV outcomes in coinfected HAART recipients. *AIDS*. 2009;23(14):1881-1889.
5. Bellini C, Keiser O, Chave JP, et al. Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study. *HIV Med*. 2009;10(1):12-18.
6. Law WP, Dore GJ, Duncombe CJ, et al. Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996-2001. *AIDS*. 2003;17(15):2191-2199.
7. Wit FW, Weverling GJ, Weel J, et al. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis*. 2002;186(1):23-31.
8. Dore GJ, Soriano V, Rockstroh J, et al. Frequent hepatitis B virus rebound among HIV-hepatitis B virus-coinfected patients following antiretroviral therapy interruption. *AIDS*. 2010;24(6):857-865.
9. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir - effects on HIV-1 replication and resistance. *N Engl J Med*. 2007;356(25):2614-2621.
10. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. *Hepatology*. 1999;30(5):1302-1306.
11. Manegold C, Hannoun C, Wywiol A, et al. Reactivation of hepatitis B virus replication accompanied by acute hepatitis in patients receiving highly active antiretroviral therapy. *Clin Infect Dis*. 2001;32(1):144-148.
12. Sulkowski MS, Thomas DL, Chaisson RE, et al. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA*. 2000;283(1):74-80.
13. den Brinker M, Wit FW, Wertheim-van Dillen PM, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS*. 2000;14(18):2895-2902.
14. Centers for Disease Control and Prevention (CDC). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009;58(RR-4):1-207.
15. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):661-662.
16. Woo G, Tomlinson G, Nishikawa Y, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. *Gastroenterology*. 2010;139(4):1218-1229.

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

17. Peters MG, Andersen J, Lynch P, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. *Hepatology*. 2006;44(5):1110-1116.

18. Matthews GV, Seaberg E, Dore GJ, et al. Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV coinfected individuals. *AIDS*. 2009;23(13):1707-1715.

19. de Vries-Sluijs TE, Reijnders JG, Hansen BE, et al. Long-Term Therapy with Tenofovir is Effective for Patients Co-Infected with HIV and HBV. *Gastroenterology*. 2010.

20. Pessoa MG, Gazzard B, Huang AK, et al. Efficacy and safety of entecavir for chronic HBV in HIV/HBV coinfected patients receiving lamivudine as part of antiretroviral therapy. *AIDS*. 2008;22(14):1779-1787.

21. Benhamou Y, Bochet M, Thibault V, et al. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. *Lancet*. 2001;358(9283):718-723.

22. Ingiliz P, Valantin MA, Thibault V, et al. Efficacy and safety of adefovir dipivoxil plus pegylated interferon-alpha2a for the treatment of lamivudine-resistant hepatitis B virus infection in HIV-infected patients. *Antivir Ther*. 2008;13(7):895-900.

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

HIV/Hepatitis C Virus (HCV) Coinfection (Last updated March 27, 2012; last reviewed March 27, 2012)

Key Considerations When Managing Patients Coinfected with HIV and Hepatitis C Virus

- All HIV-infected patients should be screened for hepatitis C virus (HCV) infection, preferably before starting antiretroviral therapy (ART).
- ART may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation. For most HIV/HCV-coinfected patients, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury (DILI). Therefore, ART should be considered for HIV/HCV-coinfected patients, regardless of CD4 count **(BII)**.
- Initial ART combination regimens for most HIV/HCV-coinfected patients are the same as those for individuals without HCV infection. However, when treatment for both HIV and HCV is indicated, consideration of potential drug-drug interactions and overlapping toxicities should guide ART regimen selection or modification (see discussion in the text).
- Combined treatment of HIV and HCV can be complicated by large pill burden, drug interactions, and overlapping toxicities. Although ART should be initiated for most HIV/HCV-coinfected patients regardless of CD4 cell count, in ART-naive patients with CD4 counts >500 cells/mm^3 some clinicians may choose to defer ART until completion of HCV treatment.
- In patients with lower CD4 counts (e.g., <200 cells/mm^3), it may be preferable to initiate ART and delay HCV therapy until CD4 counts increase as a result of ART.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion*

Approximately one-third of patients with chronic hepatitis C virus (HCV) infection progress to cirrhosis at a median time of less than 20 years.[1, 2] The rate of progression increases with older age, alcoholism, male sex, and HIV infection.[3-6] In a meta-analysis, individuals coinfected with HIV/HCV were found to have three times greater risk of progression to cirrhosis or decompensated liver disease than were HCV-monoinfected patients.[5] This accelerated rate is magnified in HIV/HCV-coinfected patients with low CD4 counts. Although ART appears to slow the rate of HCV disease progression in HIV/HCV-coinfected patients, several studies have demonstrated that the rate continues to exceed that observed in those without HIV infection.[7, 8] Whether HCV infection accelerates HIV progression, as measured by AIDS-related opportunistic infections (OIs) or death,[9] is unclear. If such an increased risk of HIV progression exists, it may reflect the impact of injection drug use, which is strongly linked to HCV infection.[10,11] The increased frequency of antiretroviral (ARV)-associated hepatotoxicity with chronic HCV infection also complicates HIV treatment.[12, 13]

A combination regimen of peginterferon and ribavirin (PegIFN/RBV) has been the mainstay of treatment for HCV infection. In HCV genotype 1-infected patients without HIV, addition of an HCV NS3/4A protease inhibitor (PI) boceprevir or telaprevir to PegIFN/RBV significantly improves the rate of sustained virologic response (SVR).[14, 15] Clinical trials of these HCV PIs in combination with PegIFN/RBV for the treatment of HCV genotype 1 infection in HIV-infected patients are currently under way. Both boceprevir and telaprevir are substrates and inhibitors of cytochrome P (CYP) 3A4/5 and p-glycoprotein (p-gp); boceprevir is also metabolized by aldo-keto reductase. These drugs have significant interactions with certain ARV drugs that are metabolized by the same pathways. As such, the presence of HCV infection and the treatment of HCV may influence HIV treatment as discussed below.

Assessment of HIV/Hepatitis C Virus Coinfection Before Initiation of Antiretroviral Therapy

- All HIV-infected patients should be screened for HCV infection using sensitive immunoassays licensed for detection of antibody to HCV in blood.[16] HCV-seronegative patients at risk for the acquistion of HCV

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

infection should undergo repeat testing annually. HCV-seropositive patients should be tested for HCV RNA using a qualitative or quantitative assay to confirm the presence of active infection.[17]

- Patients with HIV/HCV coinfection should be counseled to avoid consuming alcohol and to use appropriate precautions to prevent transmission of HIV and/or HCV to others. HIV/HCV-coinfected patients who are susceptible to hepatitis A virus (HAV) or hepatitis B virus (HBV) infection should be vaccinated against these viruses.
- All patients with HIV/HCV coinfection should be evaluated for HCV therapy. HCV treatment is recommended according to standard guidelines.[18, 19] Strong preference should be given to commence HCV treatment in patients with higher CD4 counts. For patients with lower CD4 counts (e.g., <200 cells/mm^3), it may be preferable to initiate ART and delay HCV therapy until CD4 counts increase as a result of HIV treatment.[17, 20-22]

Antiretroviral Therapy in HIV/Hepatitis C Virus Coinfection

- When to start antiretroviral therapy: The rate of liver disease (liver fibrosis) progression is accelerated in HIV/HCV-coinfected patients, particularly in individuals with low CD4 counts (≤350 cells/mm^3). Data largely from retrospective cohort studies are inconsistent regarding the effect of ART on the natural history of HCV disease.[6, 23, 24] However, ART may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation.[25-27] Thus, for most coinfected patients, including those with high CD4 counts and those with cirrhosis, the benefits of ART outweigh concerns regarding DILI. Therefore, ART should be initiated for most HIV/HCV-coinfected patients, regardless of CD4 count **(BII)**. However, in HIV treatment-naive patients with CD4 counts >500 cells/mm^3, some clinicians may choose to defer ART until completion of HCV treatment.
- What antiretroviral to start and what antiretroviral not to use: Initial ARV combination regimens for most HIV treatment-naive patients with HCV are the same as those for patients without HCV infection. Special considerations for ARV selection in HIV/HCV-coinfected patients include:
  - When both HIV and HCV treatments are indicated, the choice of ARV regimen should be guided by the HCV treatment regimen selected with careful consideration of potential drug-drug interactions and overlapping toxicities (as discussed below).
  - Cirrhotic patients should be carefully assessed for signs of liver decompensation according to the Child-Turcotte-Pugh classification system because hepatically metabolized ARV drugs may require dose modification or avoidance in patients with Child-Pugh class B and C disease. (See Appendix B, Table 7.)
- Hepatotoxicity: DILI following initiation of ART is more common in HIV/HCV-coinfected patients than in those with HIV monoinfection. The greatest risk of DILI may be observed in coinfected individuals with advanced liver disease (e.g., cirrhosis or end-stage liver disease).[28] Eradication of HCV infection with treatment may decrease the likelihood of ARV-associated DILI.[29]
  - Given the substantial heterogeneity in patient populations and drug regimens, comparison of DILI incidence rates for individual ARV agents across clinical trials is difficult. In such studies, the highest incidence rates of significant elevations in liver enzyme levels (>5 times the upper limit of the laboratory reference range) have been observed during therapy with ARV drugs that are no longer commonly used in clinical practice, including stavudine (d4T) (with or without didanosine [ddI]), nevirapine (NVP), or full-dose ritonavir (RTV) (600 mg twice daily).[30] Additionally, certain ARV agents should be avoided if possible because they have been associated with higher incidence of serious liver-associated adverse effects, such as fatty liver disease with nucleoside reverse transcriptase inhibitors (NRTIs) such as d4T, ddI, or zidovudine (ZDV);[31] noncirrhotic portal hypertension associated with ddI;[32] and hepatotoxicity associated with RTV-boosted tipranavir.[33]

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored at 1 month after initiation of ART and then every 3 to 6 months. Mild to moderate fluctuations in ALT and/or AST are typical in individuals with chronic HCV infection. In the absence of signs and/or symptoms of liver disease these fluctuations do not require interruption of ART. Significant ALT and/or AST elevation should prompt careful evaluation for signs and symptoms of liver insufficiency and for alternative causes of liver injury (e.g., acute HAV or HBV infection, hepatobiliary disease, or alcoholic hepatitis); short-term interruption of the ART regimen or of the specific drug suspected to be responsible for the DILI may be required.[34]

Treating Both HIV and Hepatitis C Virus Infection

Concurrent treatment of HIV and HCV is feasible but may be complicated by high pill burden, drug interactions, and overlapping drug toxicities. In this context, the decision to treat chronic HCV should also include consideration of the medical need for such treatment on the basis of an assessment of HCV disease stage. Some clinicians may choose to defer HCV therapy in HIV/HCV-coinfected patients with no or minimal liver fibrosis. If treatment with PegIFN/RBV alone or in combination with one of the HCV NS3/4A PIs (boceprevir or telaprevir) is initiated, the ART regimen may need to be modified to reduce the potential for drug interactions and/or toxicities that may develop during the period of concurrent HIV and HCV treatment.

Considerations for using certain nucleoside reverse transcriptase inhibitors and hepatitis C virus treatments:

- ddI **should not be given** with RBV because of the potential for drug-drug interactions leading to life-threatening ddI-associated mitochondrial toxicity including hepatomegaly/steatosis, pancreatitis, and lactic acidosis **(AII)**.[35]
- Combined use of ZDV and RBV is associated with increased rates of anemia, making RBV dose reduction necessary. Therefore, this combination should be avoided when possible.[36] Because the risk of anemia may further increase when boceprevir or telaprevir is combined with PegIFN/RBV, ZDV **should not be given** with this combination **(AIII)**.
- Abacavir (ABC) has been associated with decreased response to PegIFN/RBV in some, but not all, retrospective studies; current evidence is insufficient to recommend avoiding this combination.[37-39]

Considerations for the use of HCV NS3/4A protease inhibitors (boceprevir or telaprevir) and antiretroviral therapy:

- Boceprevir is approved for the treatment of HCV genotype 1 infection in patients without HIV infection. After 4 weeks of PegIFN/RBV therapy, boceprevir is added to the regimen for 24, 32, or 44 additional weeks of HCV therapy. Data on the use of an HCV regimen containing boceprevir together with ART in HIV/HCV-coinfected individuals are limited. In 1 small study of coinfected patients, higher HCV response was observed with boceprevir plus PegIFN/RBV (64 patients) than with PegIFN/RBV alone (34 patients). In this study, patients received ART that included HIV-1 ritonavir-boosted atazanavir (ATV/r), darunavir (DRV/r), or lopinavir (LPV/r) or raltegravir (RAL) plus dual NRTIs.[40]

  Boceprevir is primarily metabolized by aldo-keto reductase, but because the drug is also a substrate and inhibitor of CYP3A4/5 and p-gp enzymes, it may interact with ARVs metabolized by these pathways. Based on drug interaction studies in healthy volunteers, boceprevir can be coadministered with RAL.[41] However, coadministration of boceprevir with ATV/r, DRV/r, LPV/r, or efavirenz (EFV) is not recommended because of bidirectional drug interactions (see Table 15a and 15b).[42, 43] Importantly, the pharmacokinetic (PK) interactions of HIV PIs with boceprevir were not identified before the approval of boceprevir and before participant enrollment in the HIV/HCV-coinfection trial; consequently, some

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

coinfected patients have received HIV PIs and boceprevir during HCV treatment. Patients who are currently receiving these drug combinations should be advised not to stop any medication until contacting their health care providers. If therapy with HIV PIs and boceprevir is continued, patients should be closely monitored for HIV and HCV responses and consideration should be given to switching the HIV PI or EFV to RAL during boceprevir therapy. Additional clinical trial data are needed to determine if other ARVs may be coadministered with boceprevir.

- Telaprevir is approved for the treatment of HCV genotype 1 infection in patients without HIV infection. Telaprevir is administered in combination with PegIFN/RBV for the initial 12 weeks of HCV therapy followed by 12 or 36 weeks of additional treatment with PegIFN/RBV. Data on the use of this regimen in HIV/HCV-coinfected individuals are limited. In 1 small study of coinfected patients, higher HCV response was observed with telaprevir plus PegIFN/RBV (38 patients) than with PegIFN/RBV alone (22 patients). In this study, patients received ART containing EFV or ATV/r plus tenofovir/emtricitabine (TDF/FTC) or no ART during the HCV therapy.[44]

  Because telaprevir is a substrate and an inhibitor of CYP3A4 and p-gp enzymes, the drug may interact with ARVs metabolized by these pathways. On the basis of drug interaction studies in healthy volunteers and data on responses in coinfected patients enrolled in the small clinical trial noted above, telaprevir can be coadministered with ATV/r[45] and RAL[46] at the standard recommended dose of telaprevir (750 mg every 7–9 hours) and with EFV at an increased dose of telaprevir (1125 mg every 7–9 hours) (see Table 15b); however, coadministration of telaprevir with DRV/r, fosamprenavir/ritonavir (FPV/r), or LPV/r is not recommended because of bidirectional drug interactions.[45] Data on PK interactions of telaprevir with other ARVs including non-nucleoside reverse transcriptase inhibitors (NNRTIs) other than EFV and with maraviroc (MVC) are not available; therefore, coadministration of telaprevir with other ARVs cannot be recommended.

Following are preliminary recommendations for the use of boceprevir or telaprevir in HIV patients coinfected with HCV genotype 1 based on current ART use. These recommendations may be modified as new drug interaction and clinical trial information become available.

Patients not on ART:	Use either boceprevir or telaprevir
Patients receiving RAL + 2-NRTI:	Use either boceprevir or telaprevir
Patients receiving ATV/r + 2-NRTI:	Use telaprevir at standard dose. Do not use boceprevir.
Patients receiving EFV + 2-NRTI:	Use telaprevir at increased dose of 1125 mg every 7–9 hours. Do not use boceprevir.

Patients receiving other ARV regimens:

- If HCV disease is minimal (i.e., no or mild portal fibrosis), consider deferring HCV treatment given rapidly evolving HCV drug development.
- If good prognostic factors for HCV treatment response are present—IL28B CC genotype or low HCV RNA level (<400,000 International Unit [IU]/mL)—consider use of PegIFN/RBV without HCV NS3/4A PI.
- On the basis of ART history and HIV genotype testing results, if possible, consider switching to the ART regimens listed above to permit the use of boceprevir or telaprevir.
- For patients with complex ART history or resistance to multiple classes of ART, consultation with experts regarding the optimal strategy to minimize the risk of HIV breakthrough may be needed. In such patients, telaprevir may be the preferred HCV NS3/4A PI because its duration of use (12 weeks) is shorter than that of boceprevir (24 to 44 weeks).

Summary:

In summary, HCV coinfection and use of PegIFN/RBV with or without HCV NS3/4A PIs (telaprevir or boceprevir) to treat HCV may impact the treatment of HIV because of increased pill burden, toxicities, and

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

drug-drug interactions. Because ART may slow the progression of HCV-related liver disease, ART should be considered for most HIV/HCV-coinfected patients, regardless of CD4 count. If treatment with PegIFN/RBV alone or in combination with one of the HCV NS3/4A PIs (telaprevir or boceprevir) is initiated, the ART regimen may need to be modified to reduce the potential for drug-drug interactions and/or drug toxicities that may develop during the period of concurrent HIV and HCV treatment. The science of HCV drug development is evolving rapidly. As new clinical trial data on the management of HIV/HCV-coinfected patients with newer HCV drugs become available, the Panel will modify its recommendations accordingly.

References

1. Alter MJ, et al. The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team. *N Engl J Med*. 1992;327(27):1899-1905.
2. Thomas DL, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA*. 2000;284(4):450-456.
3. Poynard T, Bedossa B, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet*. 1997;349(9055):825-832.
4. Wiley TE, et al. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology*. 1998;28(3):805-809.
5. Graham CS, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis*. 2001;33(4):562-569.
6. Thein HH, et al. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS*. 2008;22(15):1979-1991.
7. Weber R, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. 2006;166(15):1632-1641.
8. Kitahata MM, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. 2009;360(18):1815-1826.
9. Greub G, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet*. 2000;356(9244):1800-1805.
10. Vlahov D, et al. Prognostic indicators for AIDS and infectious disease death in HIV-infected injection drug users: plasma viral load and CD4+ cell count. *JAMA*. 1998; 279(1):35-40.
11. Celentano DD, et al. Self-reported antiretroviral therapy in injection drug users. *JAMA*. 1998;280(6):544-546.
12. Sulkowski MS, et al. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA*. 2000;283(1):74-80.
13. Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology*. 2002;35(1):182-189.
14. Poordad F, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364(13):1195-1206.
15. Jacobson IM, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med*. 2011;364(25):2405-2416.
16. Centers for Disease Control and Prevention (CDC). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009;58(RR-4):1-207.
17. Ghany MG, et al. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009;49(4):1335-1374.
18. Ghany MG, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54(4):1433-1444.

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

19. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV/AIDS. Department of Health and Human Services. 2012 (In Press).
20. Soriano V, et al. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. *AIDS*. 2007;21(9):1073-1089.
21. Tien PC. Management and treatment of hepatitis C virus infection in HIV-infected adults: recommendations from the Veterans Affairs Hepatitis C Resource Center Program and National Hepatitis C Program Office. *Am J Gastroenterol*. 2005;100(10):2338-2354.
22. Avidan NU, et al. Hepatitis C Viral Kinetics During Treatment With Peg IFN-alpha-2b in HIV/HCV Coinfected Patients as a Function of Baseline CD4+ T-Cell Counts. *J Acquir Immune Defic Syndr*. 2009;52(4):452-458.
23. Sulkowski MS, et al. Rapid fibrosis progression among HIV/hepatitis C virus-co-infected adults. *AIDS*. 2007;21(16): 2209-2216.
24. Brau N, et al. Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy. *J Hepatol*. 2006;44(1):47-55.
25. Macias J, et al. Fast fibrosis progression between repeated liver biopsies in patients coinfected with human immunodeficiency virus/hepatitis C virus. *Hepatology*. 2009;50(4):1056-1063.
26. Verma S, Goldin RD, Main J. Hepatic steatosis in patients with HIV-Hepatitis C Virus coinfection: is it associated with antiretroviral therapy and more advanced hepatic fibrosis? *BMC Res Notes*. 2008;1:46.
27. Ragni MV, et al. Highly active antiretroviral therapy improves ESLD-free survival in HIV-HCV co-infection. *Haemophilia*. 2009;15(2):552-558.
28. Aranzabal L, et al. Influence of liver fibrosis on highly active antiretroviral therapy-associated hepatotoxicity in patients with HIV and hepatitis C virus coinfection. *Clin Infect Dis*. 2005;40(4):588-593.
29. Labarga P, et al. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-infected patients. *J Infect Dis*. 2007;196(5):670-676.
30. Nunez M. Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. *J Hepatol*. 2006;44(1 Suppl):S132-S139.
31. McGovern BH, et al. Hepatic steatosis is associated with fibrosis, nucleoside analogue use, and hepatitis C virus genotype 3 infection in HIV-seropositive patients. *Clin Infect Dis*. 2006;43(3):365-372.
32. Kovari H, et al. Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case-control study. *Clin Infect Dis*. 2009;49(4):626-635.
33. Food and Drug Administration. Aptivus (package insert). http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021814s011lbl.pdf. Accessed March 26, 2012.
34. Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected patient. *Clin Liver Dis*. 2003;7(1):179-194.
35. Fleischer R, Boxwell D, Sherman KE. Nucleoside analogues and mitochondrial toxicity. *Clin Infect Dis*. 2004;38(8):e79-e80.
36. Alvarez D, et al. Zidovudine use but not weight-based ribavirin dosing impacts anaemia during HCV treatment in HIV-infected persons. *J Viral Hepat*. 2006;13(10):683-689.
37. Vispo E, et al. Low response to pegylated interferon plus ribavirin in HIV-infected patients with chronic hepatitis C treated with abacavir. *Antivir Ther*. 2008;13(3):429-437.
38. Laufer N, et al. Abacavir does not influence the rate of virological response in HIV-HCV-coinfected patients treated with pegylated interferon and weight-adjusted ribavirin. *Antivir Ther*. 2008;13(7):953-957.
39. Mira JA, et al. Efficacy of pegylated interferon plus ribavirin treatment in HIV/hepatitis C virus co-infected patients receiving abacavir plus lamivudine or tenofovir plus either lamivudine or emtricitabine as nucleoside analogue backbone. *J Antimicrob Chemother*. 2008;62(6):1365-1373.

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

40. Sulkowski, M., S. Pol, et al. (2012). Boceprevir + pegylated interferon + ribavirin for the treatment of HCV/HIV coinfected patients: End of treatment (Week 48) interim results. 18th Conference on Retroviruses and Opportunistic Infections. Seattle, WA, Abs 47.
41. de Kanter CB, Blonk M, Colbers A, Fillekes Q, Schouwenberg B, Burger D. The Influence of the HCV Protease Inhibitor Bocepravir on the Pharmocokinetics of the HIV Integrase Inhibitor Raltegravir. Paper presented at: 19th Conference on Retroviruses and Opportunistic Infections (CROI);March 5-8, 2012; Seattle, WA.
42. Hulskotte E, Feng H-P, Xuan F, van Zutven M, O'Mara E, Youngberg S, Wagner J, Butterton J. Pharmacokinetic interaction between the HCV protease inhibitor bocepravir and ritonavir-boosted HIV-1 protease inhibitors atazanavir, lopinavir, and darunavir. Paper presented at: 19th Conference on Retroviruses and Opportunistic Infections (CROI); March 5-8, 2012; Seattle, WA.
43. Food and Drug Administration, Victrelis (package insert). http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202258lbl.pdf. Accessed March 23, 2012.
44. Dieterich D., V. Soriano, et al. (2012). Telaprevir in combination with peginterferion a-2a + ribavirin in HCV/HIV-coinfected patients: a 24-week treatment interim analysis. 18th Conference on Retroviruses and Opportunistic Infections. Seattle, WA, Abs 46.
45. Food and Drug Administration, INCIVEK (package insert). Accessed March 23, 2012.
46. van Heeswijk R, et al. The pharmacokinetic interaction between telaprevir and raltegravir in healthy volunteers. Paper presented at:51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 17-20, 2011; Chicago, IL.

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

Mycobacterium Tuberculosis Disease with HIV Coinfection (Last updated March 27, 2012; last reviewed March 27, 2012)

Panel's Recommendations
• The principles for treatment of active tuberculosis (TB) disease in HIV-infected patients are the same as those for HIV-uninfected patients **(AI)**.
• All HIV-infected patients with diagnosed active TB should be started on TB treatment immediately **(AI)**.
• All HIV-infected patients with diagnosed active TB should be treated with antiretroviral therapy (ART) **(AI)**.
• In patients with CD4 counts <50 cells/mm^3, ART should be initiated within 2 weeks of starting TB treatment **(AI)**.

• In patients with CD4 counts ≥50 cells/mm^3 who present with clinical disease of major severity as indicated by clinical evaluation (including low Karnofsky score, low body mass index [BMI], low hemoglobin, low albumin, organ system dysfunction, or extent of disease), ART should be initiated within 2 to 4 weeks of starting TB treatment. The strength of this recommendation varies on the basis of CD4 cell count:
  • CD4 count 50 to 200 cells/mm^3 **(BI)**
  • CD4 count >200 cells/mm^3 **(BIII)**

• In patients with CD4 counts ≥50 cells/mm^3 who do not have severe clinical disease, ART can be delayed beyond 2 to 4 weeks of starting TB therapy but should be started within 8 to 12 weeks of TB therapy initiation. The strength of this recommendation also varies on the basis of CD4 cell count:
  • CD4 count 50 to 500 cells/mm^3 **(AI)**
  • CD4 count >500 cells/mm^3 **(BIII)**

• In all HIV-infected pregnant women with active TB, ART should be started as early as feasible, both for maternal health and for prevention of mother-to-child transmission (PMTCT) of HIV **(AIII)**.
• In HIV-infected patients with documented multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, ART should be initiated within 2 to 4 weeks of confirmation of TB drug resistance and initiation of second-line TB therapy **(BIII)**.
• Despite pharmacokinetic drug interactions, a rifamycin (rifampin or rifabutin) should be included in TB regimens for patients receiving ART, with dosage adjustment if necessary **(AII)**.
• Rifabutin is the preferred rifamycin to use in HIV-infected patients with active TB disease on a protease inhibitor (PI)-based regimen because the risk of substantial drug interactions with PIs is lower with rifabutin than with rifampin **(AII)**.
• Coadministration of rifampin and PIs (with or without ritonavir [RTV] boosting) is not recommended **(AII)**.
• Rifapentine (RPT) is NOT recommended in HIV-infected patients receiving ART for treatment of latent TB infection (LTBI) or active TB, unless in the context of a clinical trial **(AIII)**.
• Immune reconstitution inflammatory syndrome (IRIS) may occur after initiation of ART. Both ART and TB treatment should be continued while managing IRIS **(AIII)**.
• Treatment support, which can include directly observed therapy (DOT) of TB treatment, is strongly recommended for HIV-infected patients with active TB disease **(AII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion*

Treatment of Active Tuberculosis in HIV-Infected Patients

HIV infection significantly increases the risk of progression from latent to active TB disease. The CD4 cell count influences both the frequency and severity of active TB disease.[1-2] Active TB also negatively affects

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

HIV disease. It may be associated with a higher HIV viral load and more rapid progression of HIV disease.[3]

Active pulmonary or extrapulmonary TB disease requires prompt initiation of TB treatment. The treatment of active TB disease in HIV-infected patients should follow the general principles guiding treatment for individuals without HIV **(AI)**. Treatment of drug-susceptible TB disease should include a standard regimen that consists of isoniazid (INH) + a rifamycin (rifampin or rifabutin) + pyrazinamide + ethambutol given for 2 months, followed by INH + a rifamycin for 4 to 7 months.[4] The Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents[4] include a more complete discussion of the diagnosis and treatment of TB disease in HIV-infected patients.

All patients with HIV/TB disease should be treated with ART **(AI)**. Important issues related to the use of ART in patients with active TB disease include: (1) when to start ART, (2) significant pharmacokinetic drug-drug interactions between rifamycins and some antiretroviral (ARV) agents, (3) the additive toxicities associated with concomitant ARV and TB drug use, (4) the development of TB-associated IRIS after ART initiation, and (5) the need for treatment support including DOT and the integration of HIV and TB care and treatment.

Antiretroviral Therapy in Patients with Active Tuberculosis

Patients Diagnosed with Tuberculosis While Receiving Antiretroviral Therapy

When TB is diagnosed in a patient receiving ART, the patient's ARV regimen should be assessed with particular attention to potential pharmacokinetic interactions with rifamycins (discussed below). The patient's regimen may need to be modified to permit use of the optimal TB treatment regimen (see Tables 14–16 for dosing recommendations).

Patients Not Yet Receiving Antiretroviral Therapy

Until recently, when to start ART in patients with active TB has been a subject of debate. Survival is improved when ART is started early following initiation of TB therapy, but a delay in initiating ART often was favored because of the potential complications of high pill burden, additive toxicities, drug interactions, adherence, and the potential for development of IRIS.Recent studies primarily conducted in resource-limited settings, including three randomized controlled trials, have helped clarify the question of when to start ART in patients with active TB.[5-8]

The SAPiT study conducted in South Africa convincingly demonstrated that starting ART during rather than after concluding treatment for TB can significantly reduce mortality. In this study, ambulatory HIV-infected patients with smear-positive TB and CD4 counts <500 cells/mm^3 were randomized to one of three treatment arms: integrated therapy with ART initiated either during the first 4 weeks of TB therapy or after the first 8 weeks of TB treatment (i.e., during the continuation phase of TB therapy) or sequential therapy with ART initiated after the conclusion of standard TB therapy. The median CD4 cell count of participants at study entry was 150 cells/mm^3. The sequential therapy arm was stopped when an early analysis demonstrated that the mortality rate in the combined two integrated arms was 56% lower than the rate in the sequential therapy arm. Treatment was continued in the two integrated arms until study completion.[5]

With the completion of SAPiT and 2 other randomized controlled trials, CAMELIA and STRIDE, the question on the optimal time to initiate ART during TB therapy has been addressed. Findings from these trials now serve as the basis for the Panel's recommendations on when to start ART in patients with active TB.

In the final analysis of the SAPiT trial, there were no differences in rates of AIDS or death between the 2 integrated arms of the study (patients who started ART within 4 weeks after initiating TB treatment vs. those who started ART at 8–12 weeks [i.e., within 4 weeks after completing the intensive phase of TB treatment]).

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

However, in patients with baseline CD4 counts <50 cells/mm^3 (17% of the study population), the rate of AIDS or death was lower in the earlier therapy group than in the later therapy group (8.5 vs. 26.3 cases per 100 person-years, a strong trend favoring the earlier treatment arm, $P = 0.06$). For all patients, regardless of CD4 cell count, earlier therapy was associated with a higher incidence of IRIS and of adverse events that required a switch in ARV drugs than later therapy. Two deaths were attributed to IRIS.[6]

In the CAMELIA study, which was conducted in Cambodia[7], patients who had CD4 counts <200 cells/mm^3 were randomized to initiate ART at 2 weeks or 8 weeks after initiation of TB treatment. Study participants had advanced HIV disease, with a median entry CD4 count of 25 cells/mm^3; low BMIs (median = 16.8 kg/m^2), Karnofsky scores (87% <70), and hemoglobin levels (median = 8.7 g/dl); and high rates of disseminated TB disease. Compared with therapy initiated at 8 weeks, ART initiated at 2 weeks resulted in a 38% reduction in mortality ($P = 0.006$). A significant reduction in mortality was seen in patients with CD4 counts ≤50 cells/mm^3 and in patients with CD4 counts 51 to 200 cells/mm^3. Overall, 6 deaths associated with TB-IRIS were reported.

The ACTG 5221 (STRIDE) trial, a multinational study conducted at 28 sites, randomized ART-naive patients with confirmed or probable TB and CD4 counts <250 cells/mm^3 to earlier (<2 weeks) or later (8–12 weeks) ART.[8] At study entry, the participants' median CD4 count was 77 cells/mm^3. The rates of mortality and AIDS diagnoses were not different between the earlier and later arms, although higher rates of IRIS were seen in the earlier arm. However, a significant reduction in AIDS or death was seen in the subset of patients with CD4 counts <50 cells/mm^3 who were randomized to the earlier ART arm ($P = 0.02$).

In each of these 3 studies, IRIS was more common in patients initiating ART earlier than in patients starting ART later, but the syndrome was infrequently associated with mortality. Collectively these 3 trials demonstrate that in patients with active TB and with very low CD4 cell counts (i.e., <50 cells/mm^3), early initiation of ART can reduce mortality and AIDS progression, albeit at the risk of increased IRIS. These findings strongly favor initiation of ART within the first 2 weeks of TB treatment in patients with CD4 cell counts <50 cells/mm^3 **(AI)**.

The question of when to start ART in patients with CD4 counts ≥50 cells/mm^3 is also informed by these studies. The STRIDE and SAPiT studies—in which the patients with CD4 cell counts ≥50 cells/mm^3 were relatively healthy and with reasonable Karnofsky scores (note the SAPiT study excluded patients with Karnofsky scores <70) and BMIs—demonstrated that ART initiation in these patients can be delayed until 8 to 12 weeks after initiation of TB therapy (**AI** for CD4 counts 51–500 cells/mm^3 and **BIII** for CD4 counts >500 cells/mm^3).

However, the CAMELIA study, which included more patients who were severely ill than the STRIDE and SAPiT studies, showed that early initiation of ART improved survival both in patients with CD4 counts ≤50 cells/mm^3 and in patients with CD4 counts from 51 to 200 cells/mm^3. In a multivariate analysis, age >40 years, low BMI (<16), low Karnofsky score (<40), elevated aspartate aminotransferase (AST) level (>1.25 x the upper limit of normal [ULN]), disseminated and MDR TB were independently associated with poor survival; whereas in a univariate analysis, hemoglobin <10g/dl also was associated with poor survival.

Thus, recently published results from the three clinical trials are complementary in defining the need for ART and use of CD4 count and clinical status to inform decisions on the optimal time to initiate ART in patients with HIV and TB disease. Earlier initiation of ART within 2 to 4 weeks of TB treatment should be strongly considered for patients with CD4 cell counts from 50 to 200 cells/mm^3 who have evidence of clinical disease of major severity as indicated by clinical evaluation, low Karnofsky score, low BMI, low hemoglobin, low albumin, or organ system dysfunction **(BI)**. Initiation of ART within 2 to 4 weeks also should be considered for patients with CD4 counts >200 cells/mm^3 who present with evidence of severe disease **(BIII)**.

Of additional importance, each of the above studies demonstrated excellent responses to ART, with 90% and >95% of participants achieving suppressed viremia (HIV RNA <400 copies/mL) at 12 months in the SAPiT

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

and CAMELIA studies, respectively, and 74% of participants at 2 years in the STRIDE study.

Mortality rates in patients with MDR or XDR TB and HIV coinfection are very high.[9] Retrospective case control studies and case series provide growing evidence of better outcomes associated with receipt of ART in such coinfected patients,[10] but the optimal timing for initiation of ART is unknown. However, given the high rates and rapid mortality, most experts recommend that ART be initiated within 2 to 4 weeks after confirmation of the diagnosis of drug resistance and initiation of second-line TB therapy **(BIII)**.

All HIV-infected pregnant women with active TB should be started on ART as early as feasible, both for maternal health and to prevent perinatal transmission of HIV **(AIII)**. The choice of ART should be based on efficacy and safety in pregnancy and take into account potential drug-drug interactions between ARVs and rifamycins (see Perinatal Guidelines for more detailed discussions).[11]

TB meningitis often is associated with severe complications and high mortality rate. In a randomized study conducted in Vietnam, patients were randomized to immediate ART or to therapy deferred until 2 months after initiation of TB treatment. A higher rate of severe (Grade 4) adverse events was seen in patients who received immediate ART than in those who deferred therapy (80.3% vs. 69.1%, respectively; $P = 0.04$).[12] In this study 59.8% of the immediate ART patients and 55.5% of the delayed ART patients died within 9 months. However, in the United States, where patients may be more closely monitored and treated for severe adverse events such as central nervous system (CNS) IRIS, many experts feel that ART should be initiated as for other HIV/TB-coinfected patients **(CIII)**.

Drug Interaction Considerations

A rifamycin is a crucial component in treatment of drug-sensitive TB. However, both rifampin and rifabutin are inducers of the hepatic cytochrome P (CYP) 450 and uridine diphosphate gluconyltransferase (UGT) 1A1 enzymes and are associated with significant interactions with most ARV agents including all PIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), maraviroc (MVC), and raltegravir (RAL). Rifampin is a potent enzyme inducer, leading to accelerated drug clearance and significant reduction in ARV drug exposure. Despite these interactions, some observational studies suggest that good virologic, immunologic, and clinical outcomes may be achieved with standard doses of efavirenz (EFV)[13-14] and, to a lesser extent, nevirapine (NVP)[15-16] when combined with rifampin. However, rifampin is not recommended in combination with all PIs and the NNRTIs etravirine (ETR) and rilpivirine (RPV). When rifampin is used with MVC or RAL, increased dosage of the ARV is generally recommended. Rifabutin, a weaker enzyme inducer, is an alternative to rifampin. Because rifabutin is a substrate of the CYP 450 enzyme system, its metabolism may be affected by the NNRTI or PI. Tables 14, 15a, 15b, 15d, and 15e outline the magnitude of these interactions and provide dosing recommendations when rifamycins and selected ARV drugs are used concomitantly. After determining the drugs and doses to use, clinicians should monitor patients closely to assure good control of both TB and HIV infections. Suboptimal HIV suppression or suboptimal response to TB treatment should prompt assessment of drug adherence, subtherapeutic drug levels (consider therapeutic drug monitoring [TDM]), and acquired drug resistance.

Rifapentine is a long-acting rifamycin that can be given once weekly with INH for the treatment of active or latent TB infection. Similar to rifampin and rifabutin, rifapentine is also a CYP3A4 inducer. No systematic study has been performed to assess the magnitude of the enzyme induction effect of rifapentine on the metabolism of ARV drugs and other concomitant drugs. Significant enzyme induction can result in reduced ARV drug exposure, which may compromise virologic efficacy. Rifapentine is **not recommended** for treatment of latent or active TB infection in patients receiving ART, unless given in the context of a clinical trial **(AIII)**.

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

Anti-Tuberculosis/Antiretroviral Drug Toxicities

ARV agents and TB drugs, particularly INH, rifamycin, and pyrazinamide, can cause drug-induced hepatitis. These first-line TB drugs should be used for treatment of active TB disease, even with coadministration of other potentially hepatotoxic drugs or when baseline liver disease is present **(AIII)**. Patients receiving potentially hepatotoxic drugs should be monitored frequently for clinical symptoms and signs of hepatitis and have laboratory monitoring for hepatotoxicity. Peripheral neuropathy can occur with administration of INH, didanosine (ddI), or stavudine (d4T) or may be a manifestation of HIV infection. All patients receiving INH also should receive supplemental pyridoxine to reduce peripheral neuropathy. Patients should be monitored closely for signs of drug-related toxicities and receive alternative ARVs to ddI or d4T.

Immune Reconstitution Inflammatory Syndrome with Tuberculosis and Antiretroviral Agents

IRIS occurs in two forms: unmasking and paradoxical. The mechanism of the syndrome is the same for both forms: restoration of immune competence by administration of ART, resulting in an exuberant host response to TB bacilli and/or antigens. Unmasking IRIS refers to the initial clinical manifestations of active TB that occurs soon after ART is started. Paradoxical IRIS refers to the worsening of TB clinical symptoms after ART is started in patients who are receiving TB treatment. Severity of IRIS ranges from mild to severe to life threatening. IRIS has been reported in 8% to more than 40% of patients starting ART after TB is diagnosed, although the incidence depends on the definition of IRIS and the intensity of monitoring.[17-18]

Predictors of IRIS include CD4 count <50 cells/mm^3; higher on-ART CD4 counts; high pre-ART and lower on-ART HIV viral loads; severity of TB disease, especially high pathogen burden; and less than 30-day interval between initiation of TB and HIV treatments.[19-22] Most IRIS in HIV/TB disease occurs within 3 months of the start of TB treatment. Delaying initiation of ART for 2 to 8 weeks may reduce the incidence and severity of IRIS. However, this possible advantage of delayed ART must be weighed against the potential benefit of earlier ART in improving immune function and preventing progression of HIV disease and mortality.

Patients with mild or moderately severe IRIS can be managed symptomatically or treated with nonsteroidal anti-inflammatory agents. Patients with more severe IRIS can be treated successfully with corticosteroids. A recent randomized, placebo-controlled trial demonstrated benefit of corticosteroids in the management of IRIS symptoms (as measured by decreasing days of hospitalization and Karnofsky performance score) without adverse consequences.[23] In the presence of IRIS, neither TB therapy nor ART should be stopped because both therapies are necessary for the long-term health of the patient **(AIII)**.

Immune Reconstitution with Antiretroviral Therapy: Conversion to Positive Tuberculin Skin Test and Interferon-Gamma Release Assay

Immune reconstitution with ART may result in unmasking LTBI (i.e., conversion of a previously negative tuberculin skin test [TST] to a positive TST or a positive interferon-gamma [IFN-γ] release assay [IGRA] for *Mycobacterium tuberculosis*-specific proteins). A positive IGRA, similar to a positive TST, is indicative of LTBI in the absence of evidence of active TB disease.[24] Because treatment for LTBI is indicated in the absence of evidence of active TB disease, clinicians should be aware of this phenomenon. Patients with a negative TST or IGRA and advanced HIV disease (i.e., CD4 count <200 cells/mm^3) should have a repeat TST or IGRA after initiation of ART and CD4 count increase to >200 cells/mm^3 **(BII)**.[25]

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

Caring for Patients with HIV and Tuberculosis

Close collaboration among clinicians, health care institutions, and public health programs involved in the diagnosis and treatment of HIV-infected patients with active TB disease is necessary in order to integrate care and improve medication adherence and TB treatment completion rates, reduce drug toxicities, and maximize HIV outcomes. HIV-infected patients with active TB disease should receive treatment support, including adherence counseling and DOT, corresponding to their needs **(AII)**. ART simplification or use of coformulated fixed-dose combinations also may help to improve drug adherence.

References

1. Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *Am Rev Respir Dis.* Nov 1993;148(5):1292-1297.
2. Perlman DC, el-Sadr WM, Nelson ET, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). *Clin Infect Dis.* Aug 1997;25(2):242-246.
3. Whalen C, Horsburgh CR, Hom D, Lahart C, Simberkoff M, Ellner J. Accelerated course of human immunodeficiency virus infection after tuberculosis. *Am J Respir Crit Care Med.* Jan 1995;151(1):129-135.
4. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* Apr 10 2009;58(RR-4):1-207; quiz CE201-204.
5. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. Feb 25 2010;362(8):697-706.
6. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med.* Oct 20 2011;365(16):1492-1501.
7. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med.* Oct 20 2011;365(16):1471-1481.
8. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med.* Oct 20 2011;365(16):1482-1491.
9. Gandhi NR, Shah NS, Andrews JR, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *Am J Respir Crit Care Med.* Jan 1 2010;181(1):80-86.
10. Dheda K, Shean K, Zumla A, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. *Lancet.* May 22 2010;375(9728):1798-1807.
11. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States, Sep. 14, 2011; pp 1-207. Available at http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf. 2011.
12. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)—associated tuberculous meningitis. *Clin Infect Dis.* Jun 2011;52(11):1374-1383.
13. Friedland G, Khoo S, Jack C, Lalloo U. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. *J Antimicrob Chemother.* Dec 2006;58(6):1299-1302.
14. Manosuthi W, Kiertiburanakul S, Sungkanuparph S, et al. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.

infected patients with tuberculosis receiving rifampicin: 48 weeks results. *AIDS.* Jan 2 2006;20(1):131-132.

15. Moses M, Zachariah R, Tayler-Smith K, et al. Outcomes and safety of concomitant nevirapine and rifampicin treatment under programme conditions in Malawi. *Int J Tuberc Lung Dis.* Feb 2010;14(2):197-202.
16. Shipton LK, Wester CW, Stock S, et al. Safety and efficacy of nevirapine- and efavirenz-based antiretroviral treatment in adults treated for TB-HIV co-infection in Botswana. *Int J Tuberc Lung Dis.* Mar 2009;13(3):360-366.
17. Haddow LJ, Moosa MY, Easterbrook PJ. Validation of a published case definition for tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS.* Jan 2 2010;24(1):103-108.
18. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis.* Aug 2008;8(8):516-523.
19. Manosuthi W, Kiertiburanakul S, Phoorisri T, Sungkanuparph S. Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculous and antiretroviral therapy. *J Infect.* Dec 2006;53(6):357-363.
20. Colebunders R, John L, Huyst V, Kambugu A, Scano F, Lynen L. Tuberculosis immune reconstitution inflammatory syndrome in countries with limited resources. *Int J Tuberc Lung Dis.* Sep 2006;10(9):946-953.
21. Michailidis C, Pozniak AL, Mandalia S, Basnayake S, Nelson MR, Gazzard BG. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. *Antivir Ther.* 2005;10(3):417-422.
22. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS.* Jan 30 2007;21(3):335-341.
23. Meintjes, G., R. J. Wilkinson, et al. (2010). Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS* 24(15): 2381-2390.
24. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. *Ann Intern Med.* Mar 6 2007;146(5):340-354.
25. Girardi E, Palmieri F, Zaccarelli M, et al. High incidence of tuberculin skin test conversion among HIV-infected individuals who have a favourable immunological response to highly active antiretroviral therapy. *AIDS.* Sep 27 2002;16(14):1976-1979.

Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2012 EST.